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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/674,892	03/26/2001	George Gow Brownlee	P02074US0	5755
26271	7590	03/08/2005	EXAMINER	
FULBRIGHT & JAWORSKI, LLP 1301 MCKINNEY SUITE 5100 HOUSTON, TX 77010-3095			WINKLER, ULRIKE	
			ART UNIT	PAPER NUMBER
			1648	

DATE MAILED: 03/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/674,892

Applicant(s)

BROWNLEE ET AL.

Examiner

Ulrike Winkler

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 24 September 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-40 and 48-60 is/are pending in the application.
- 4a) Of the above claim(s) 26 and 27 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-25, 28-40 and 48-60 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

### DETAILED ACTION

The amendment filed September 24, 2004 in response to the Office Action of March 24, 2004 is acknowledged and has been entered. Claims 57-60 have been added. Claims 1-25, 28-40, 48-60 are pending and are currently being examined.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

#### *Specification*

The Office acknowledges the receipt of the abstract.

#### *Claim Rejections - 35 USC § 101*

The rejection of claims 1-25, 28-40 and 48-60 under 35 U.S.C. 101 because the attenuated virus reads on a virus that can occur in nature wherein the virus is less virulent than another strain **is maintained**. Applicants' argument is that the duplex region of influenza virus which applicants describes as consisting of 5-8 base pairs found in the segment of the 3' and 5' non-coding terminal sequences is highly conserved. Applicants' argument is that the region is highly conserved and therefore a mutation in this region could not be naturally occurring.

Applicants' argument is not convincing. Just because an area in a genomic sequence is highly conserved does not mean that natural forces and evolution do not cause alterations in the region.

In this instance a mutation in the 3' and 5' region leads to the attenuation of the virus, it is understood that attenuated viruses replicate at a slower level when compared to wild type.

Laboratory viruses are not equivalent to viruses found in a host, some of the laboratory strain

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may not even cause disease. A virus in reality is a polymorphic population comprising a mixture of mutant where one phenotype, the ones that are successful, predominates (Kilbourne, E.D., Improving the performance of influenza and pneumococcal vaccines in adults, November 1995, Institute for Advanced Studies in Aging and Geriatric Medicine, pages 1-5). If random genome samples from a population of viruses were assayed there would be a mutant spectrum and this spectrum would harbor deleterious mutations relative to the consensus, thus generating progeny with decreased fitness (Domingo et. al. Basic Concepts in RNA virus evolution. FASEB Journal, (1996) Vol. 10, pages 859-864; see page 860, column 2, paragraph 2). Viral evolution can take the form of (1) point mutations, single base or base pair mutations (2) intramolecular recombination (3) genetic reassortment / rearrangement as seen in influenza and (4) bias hypermutations where there are more frequent uracil to cytosine transitions. Extreme viral changes tend to be lethal. A virus may not become too attenuated and survive nor too virulent because if it kills the host before transmitting to the next host the virus mutation would also not survive (see Kilbourne, E.D, page 3). Positive selection, or Darwinian selection, would imply that in a population of virus quasispecies the fitter genome suitable for replication in the new environment prevails. Negative selection operates to eliminate unfit viruses (see Domingo et. al., page 863, column 2, paragraph 2). Just because the virus may not be efficient and therefore not be the source of a potential pandemic does not mean that mutations leading to attenuation including mutations in the 3' and 5' region do not exist naturally in nature (without the interference of the hand of man). The rate of divergence of RNA viral genomes is 0.03% to 2.0% per nucleotide per year at the nucleotide level (Strauss et al. Chapter 6 Viral Evolution. In Fields Virology 3<sup>rd</sup> ed. (1996) Editors Fields et al. Lippencott-Raven Publishers, pages 153-171).

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Viral evolution indicates that only those viruses that are successful at replicating and spreading from host to host will emerge on top of the gene pool and thereby be discovered. Mutations that lead to attenuation, decreased replication, would be an example of negative selection that is predicted to occur in nature. The rejection is maintained because the claims attenuated influenza virus is not distinguishable from a virus that can occur in nature.

***Claim Rejections - 35 USC § 112***

The rejection of claims 6, 7, 25, 30, 31, 34 are 35 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention **is withdrawn** in view of applicants arguments indicating that the 20 nt at the 3' and 5' terminal region are conserved in influenza A. The specification and the art indicate that the 3' and 5' terminal region have partial inverted complementarity and this region is called the duplex region. "The postulated double stranded region of the promoter of influenza A vRNA segment is now recognized to consist of 5 to 8 base-pairs." (see specification page 3, lines 16-17).

The rejection of claims 1-25, 28-40 and 48-56 under 35 U.S.C. 112, first paragraph, **is maintained** for reason of record. It is noted that applicants have deleted the reference to functional modification in claim 1, but have not deleted the reference of functional modification in the dependent claims. Therefore, the instant invention remains rejected for reason of record.

***Claim Rejections - 35 USC § 102***

The rejection of claims 1-5, 8-24, 28, 29, 33, 37-39 and 48-56 under 35 U.S.C. 102(e) as being anticipated by Palese et al. (U.S. Pat. No. 6,022,726) **is maintained** for reasons of record.

Applicants arguments submitted September 24, 2004 have been fully considered but fail to persuade. Applicants' argument is that the reference teaches the production of chimeric virus while the instant invention is making reference to a mutated duplex region. The instant claims are drawn to a virus comprising genomic RNA as long as the virus is able to replicate and behave as an influenza virus it would fall within the claim scope.

MPEP 2111.03 The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See, e.g., *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997) ("Comprising" is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.); *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986); *In re Baxter*, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981); *Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948) ("comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts").

The claims as written do not exclude a chimeric virus. A chimeric virus which could contain the 5' region of influenza A and the 3' region of influenza B virus and would fall within the definition of being a mutated virus. There is no indication in the claim or in the specification that would exclude a chimeric virus from being a mutated virus. The ordinary molecular biologist would understand a chimeric virus to fall within the meaning of a mutated virus. There is also nothing in the claim to indicate that the mutation would require the hand of man (as discussed above see 35 U.S.C. 101 rejection). Applicants other argument is that the mutation of a base pair requires the mutation of two nucleotides. This argument is not convincing as a single

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mutation in on terminal may result in the formation of a base pair. By mutating a single amino acid to form a base pair there is a mutation in a base pair. The claims are not written in such a way to indicate that the base pair mutation requires a complementary mutation in the opposite termini.

Palese et al. disclose an attenuated genetically engineered influenza virus which contains at least one modification in the non-coding region comprising alteration to the stem structure of a promoter that down regulates synthesis of the modified viral gene segment so that some defective particles are produced (see claims 1). The attenuated virus produces subclinical infection in a patient (see claims 6). The specific example NA/B-NS shows a 5-10 fold reduced particle production (see column 14, lines 30-45). The reference also discloses the use of chimeric epitopes which results in an attenuated virus having 500-1000 fold lower LD50 levels (see column 17, lines 30-50). Therefore, the instant invention remains rejected as being anticipated by Palese et al.

The rejection of claims 1-5, 8-24, 28, 29, 33, 37-39 and 48-56 are rejected under 35 U.S.C. 102(e) as being anticipated by Palese P. (WO 93/21306) **is maintained** for reasons of record.

Applicants arguments submitted September 24, 2004 have been fully considered but fail to persuade. Applicants' argument is that the reference teaches the production of chimeric virus while the instant invention is making reference to a mutated duplex region. The instant claims are drawn to a virus comprising genomic RNA as long as the virus is able to replicate and behave as an influenza virus it would fall within the claim scope.

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MPEP 2111.03 The transitional term “comprising”, which is synonymous with “including,” “containing,” or “characterized by,” is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See, e.g., *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997) (“Comprising” is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.); *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986); *In re Baxter*, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981); *Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948) (“comprising” leaves “the claim open for the inclusion of unspecified ingredients even in major amounts”).

The claims as written do not exclude a chimeric virus. A chimeric virus which could contain the 5' region of influenza A and the 3' region of influenza B virus and would fall within the definition of being a mutated virus. There is no indication in the claim or in the specification that would exclude a chimeric virus from being a mutated virus. The ordinary molecular biologist would understand a chimeric virus to fall within the meaning of a mutated virus. There is also nothing in the claim to indicate that the mutation would require the hand of man (as discussed above see 35 U.S.C. 101 rejection). Applicants other argument is that the mutation of a base pair requires the mutation of two nucleotides. This argument is not convincing as a single mutation in on terminal may result in the formation of a base pair. By mutating a single amino acid to form a base pair there is a mutation in a base pair. The claims are not written in such a way to indicate that the base pair mutation requires a complementary mutation in the opposite termini.

Palese et al. disclose an attenuated genetically engineered influenza virus which contains at least one modification in the non-coding region comprising alteration to the stem structure of a promoter that down regulates synthesis of the modified viral gene segment so that some defective particles are produced (see claims 1-3, 6, 15-17, 20, 24, 25, 26, 27, 28). The



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attenuated virus produces subclinical infection in a patient (see claims 15-17, 20). The specific example NA/B-NS shows a 5-10 fold reduced particle production. The reference also discloses the use of chimeric epitopes which results in an attenuated virus having 500-1000 fold lower LD50 levels (see pages 35-36). Therefore, the instant invention remains rejected as being anticipated by Palese P.

The rejection of claims 1-5, 8, 9, 12-18, 20-24, 28, 29, 33 and 37 under 35 U.S.C. 102(b) as being anticipated by Bergmann et al. (Journal of General Virology, 1995, see IDS) is **maintained** for reasons of record.

Applicants arguments submitted September 24, 2004 have been fully considered but fail to persuade. Applicants' argument is that the reference teaches the production of chimeric virus while the instant invention is making reference to a mutated duplex region. The instant claims are drawn to a virus comprising genomic RNA as long as the virus is able to replicate and behave as an influenza virus it would fall within the claim scope.

MPEP 2111.03 The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See, e.g., *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997) ("Comprising" is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.); *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986); *In re Baxter*, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981); *Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948) ("comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts").

The claims as written do not exclude a chimeric virus. A chimeric virus which could contain the 5' region of influenza A and the 3' region of influenza B virus and would fall within

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the definition of being a mutated virus. There is no indication in the claim or in the specification that would exclude a chimeric virus from being a mutated virus. The ordinary molecular biologist would understand a chimeric virus to fall within the meaning of a mutated virus. There is also nothing in the claim to indicate that the mutation would require the hand of man (as discussed above see 35 U.S.C. 101 rejection). Viral evolution without any interference by man can take the form of (1) point mutations, single base or base pair mutations (2) intramolecular recombination (3) genetic reassortment / rearrangement as seen in influenza and (4) bias hypermutations where there are more frequent uracil to cytosine transitions. Any of these naturally occurring events has the potential to produce a virus that is mutated to the point of being attenuated. In this instant the cited reference mutated influenza A virus to have the same structure as an influenza B virus duplex region. Therefore, the reference anticipates the instant claims because there are 4 base pair modification for a total of 8 nucleotides that have been changed (see page 3212, column 1, paragraph 2).

Bergmann et al. disclose the construction of two influenza A virus that have mutations in the non-coding panhandle sequences (see figure 1) NA/X and NA/Y. NA/X and NA/Y both have reduced genomic RNA in infected cells (see figure 3), the RNA reduction was 5-7 fold for NA/Y and 3 fold for NA/X. These mutants were assayed for plaque formation in tissue culture using MDBK cells. The NA/Y mutant showed a 10 fold reduction compared to wild type and was found to be attenuated by at least 3 logs in the mouse inoculation assay. The reference indicates that a reduction in the expression of one viral component in the cell did not result in the packing of defective particles. The reduction in expression of one viral segment in a cell

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correlates with an attenuated viral phenotype in tissue culture and in the animal. Therefore, the instant invention is anticipated by Bergman et al.

***Claim Rejections - 35 USC § 103***

The rejection of claims 1-25, 28-40 and 48-60 under 35 U.S.C. 103(a) as being unpatentable over Bergmann et al. (Journal of General Virology, 1995), Bergmann et al. (Virus Research, 1996) and Kim et al. (Journal of General Virology, 1997) in view of Castrucci et al. (Journal of Virology, 1992) **is maintained** for reasons of record.

Applicants arguments submitted September 24, 2004 have been fully considered but fail to persuade. Applicants' argument is that the reference teaches the production of chimeric virus while the instant invention is making reference to a mutated duplex region. The instant claims are drawn to a virus comprising genomic RNA.

MPEP 2111.03 The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See, e.g., *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997) ("Comprising" is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.); *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986); *In re Baxter*, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981); *Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948) ("comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts").

The claims as written do not exclude a chimeric virus because a chimeric virus which could conceivably contain the 5' region of influenza A and the 3' region of influenza B virus would fall within the definition of being a mutated virus. In this instant the reference mutated a influenza A virus to have the same structure as the influenza B virus duplex region.

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Bergman et al. teaches the construction of two influenza A virus that have mutations in the non-coding sequences (see figure 1) NA/X and NA/Y. NA/X and NA/Y both have reduced genomic RNA in infected cells (see figure 3), the RNA reduction was 5-7 fold for NA/Y and 3 fold for NA/X. These mutants were then assayed for plaque formation in tissue culture using MDBK cells. The NA/Y mutant showed a 10 fold reduction compared to wild type and was found to be attenuated by at least 3 logs in the mouse inoculation assay. The reference indicates that a reduction in the expression of one viral component in the cell did not result in the packing of defective particles. The reduction in expression of one viral segment in a cell correlates with an attenuated viral phenotype in tissue culture and in the animal. The reference does not teach the specific mutations of the instant invention or inserting a heterologous gene into the attenuated nucleic acid construct.

Bergmann et al. teaches two influenza A/WSN/33 mutant viruses that have changes in the non-coding region of the 5' and 3' ends (see figure 1). The reference analyzed the effect of these mutation on the vRNA production in infected cells (see page 29, section 3.6). The NA/1+2 was almost 100 fold reduced as compared to the wild type virus and the partial revertants were slightly reduced. The reference teaches that the reductions in the viral titers correlate with the vRNA patterns in the cell. The reference does not teach mutations a position 11 and 10 from the 3' terminus or at position 11 and 12 from the 5' terminus.

Kim et al. teach mutations in the influenza A virus non-coding region and assays the ability to express CAT activity comparative to wild type. The reference teaches mutation in the 10-11' region of the 3' end and the 11-12' region of the 5' end (see figure 2). The mutations are

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assayed for their ability to express the protein product. The reference does not teach the correlation of reduced protein expression with an attenuated phenotype.

Castrucci et al. teach that insertion of a heterologous sequence into the neuramidase gene of influenza virus results in the attenuation of the viral construct.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the mutations that Kim et al. has shown to be effective at reducing the expression of a protein coding sequence using mutations in the promoter to produce an attenuated virus as taught by either Bergmann reference. One having ordinary skill in the art of molecular biology would have had a high expectation of success in applying the Kim et al. mutations because the art as shown in Bergmann et al. that reduced promoter activity correlates with a reduction in protein production which results in an attenuated phenotype of the virus. Adding an additional heterologous sequence into the attenuate influenza construct would be an obvious step to create a virus that exhibits an even greater attenuated phenotype. The art already has taught that insertion of a heterologous sequence into the influenza neuramidase gene will result in an attenuated phenotype. Therefore, the instant invention is obvious over both Bergmann et al. references and Kim et al. in view of Castrucci et al.

### ***Double Patenting***

The rejection of claims 1-5, 8-24, 28, 29, 33, 37-39 and 48-60 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,022,726 **is maintained**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented claims are drawn to an attenuated

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influenza virus containing at least one modified non-coding region comprising alteration to the stem loop structure which down-regulates the synthesis of one viral gene segment.

Applicants arguments submitted September 24, 2004 have been fully considered but fail to persuade. Applicants' argument is that the reference teaches the production of chimeric virus while the instant invention is making reference to a mutated duplex region. The instant claims are drawn to a virus comprising genomic RNA as long as the virus is able to replicate and behave as an influenza virus it would fall within the claim scope.

MPEP 2111.03 The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See, e.g., *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997) ("Comprising" is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.); *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986); *In re Baxter*, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981); *Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948) ("comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts").

The claims as written do not exclude a chimeric virus. A chimeric virus which could contain the 5' region of influenza A and the 3' region of influenza B virus and would fall within the definition of being a mutated virus. There is no indication in the claim or in the specification that would exclude a chimeric virus from simultaneously being a mutated virus. The ordinary molecular biologist would understand a chimeric virus to fall within the meaning of a mutated virus. Applicants other argument is that the mutation of a base pair requires the mutation of two nucleotides. This argument is not convincing as a single mutation in on terminal may result in the formation of a base pair. The claims are not written in such a way to indicate that the base pair mutation requires a complementary mutation in the opposite termini.

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***Conclusion***

No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989). The Group 1600 Official Fax number is: (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Tech Center representative whose telephone number is (571)-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 571-272-0912. The examiner can normally be reached M-F, 8:30 am - 5 pm. The examiner can also be reached via email [[ulrike.winkler@uspto.gov](mailto:ulrike.winkler@uspto.gov)].

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 571-272-0902.

  
ULRIKE WINKLER, PH.D.  
PRIMARY EXAMINER

3/7/05